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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/559,013	04/26/2000	Toshiro Ono	L0461/7086(JRV)	1882

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John R Van Amsterdam
c/o Wolf Greenfield and Sacks P C
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210-2211

EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/559,013	ONO ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *54,56,60,62,64,66,76,133 and 137* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *54,60 and 64* is/are allowed.

6)☐ Claim(s) *56,62,66,76 and 133* is/are rejected.

7)☐ Claim(s) *137* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim 134 has been canceled. Claims 54, 56, 60, 62, 64, 66, 76, 133 and 137 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 56, and 133 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 56 recites an improper Markush group. Amendment of the claim to recite "of at least 50 nucleotides, and, (b)" will overcome this rejection.

The rejection of claims 62 and 66 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 62 is drawn to an isolated expression vector comprising a nucleic acid molecule of claim 54 and a nucleic acid encoding a MHC molecule. Claim 66 is drawn to an isolated host cell transformed with the expression vector of claim 60 further comprising a nucleic acid encoding a MHC molecule. The specification teaches the treatment of diseases in a patient comprising the administration of an amount of an agent which enriches for complexes of MHC/HLA molecules and a cancer associated antigen or a fragment thereof (page 8, line 28 to page 9, line 3). Thus the specification contemplates the induction of an immune response by increasing the presence of a cancer associated antigen expressed in the context of MHC/HLA. The specification is enabling for the use of the polynucleotides encoding the cancer antigens of the invention for the detection of expressed polynucleotides to detect cancers. However, the specification is not enabling for the immunotherapy of cancer for the reasons set forth below.

The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). The specification has provided evidence that two T-cell clones are able to lyse tumor cells expressing an epitope of the claimed tumor rejection antigen precursors in vitro. Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (Nature Medicine, 1998, vol. 4, pp. 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In preclinical experiments with mice, MUC1 peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical trials a low level of CTL and a high level of humoral response was observed (Apostolopoulos, page 315, first column, bridging paragraph). Apostolopoulos et al teach that the presence of endogenous antibodies which bind to the MUC1 peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10). Apostolopoulos et al teach that mice are devoid of these antibodies (page 315, second column, lines 9-13) and are thus able to effectively mount a cellular immune response against the target antigen. Apostolopoulos et al teach that these findings have

implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion"). In support of these conclusions Jager et al (PNAS, 2000, Vol. 97, pp. 12198-12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to generate a specific T-cell response to NY-ESO after intradermal administration, whereas patients having antibodies prior to treatment which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro, and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen. These references serve to demonstrate that the induction of a anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstracts of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105) and the abstract of Algarra et al (International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of the claimed vaccine upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, the abstract of Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teaches that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules.

Paul (ibid) states that the induction of tolerance is a mechanism by which tumor cells escape immune detection. The art recognizes that T-cell are subject to clonal deletion within the thymus of a host and that this mechanism eliminates t-cell which are reactive with self-antigens. The specification teaches that the polypeptide encoded by SEQ ID NO:2 is indeed a self antigen, rather than a mutated self antigen, as it is expressed on normal tissues as well as cancerous tissues. Lauritzsen et al (International Journal of Cancer, 1998, Vol. 78, pp. 216-222) teach that clonal deletions of thymocytes is a major event in T-cell tolerance which could lead to a tumor escape mechanism. In transgenic mice homozygous for HLA-specific CD+4 T-cells which are specific for a MOPC315 plasmacytoma, injection of a large number of tumor cells results in apoptosis of immature and mature transgenic CD+4+8 and CD+4 thymocytes. This negative

selection was specific for the transgenic thymocytes that would complement the idiotype of the immunoglobulins of the MOPC315 plasmacytoma, because injection of tumor cells from a plasmacytoma which had a different idiotype of immunoglobulins failed to elicit the clonal deletion. Lauritzsen et al teach that injection of purified MOPC315 protein, versus the tumor cells, caused a profound reduction of the specific thymocytes specific to the idiotype of the plasmacytoma. Lauritzsen et al conclude that deletion of tumor specific thymocytes may represent a major escape mechanism in patients with cancers that secrete of shed antigens. In the instant case, the antigens are known self antigens. It would be reasonable to conclude that said normal antigens are presented within the thymus to developing thymocytes and T-cells with high affinity for said antigens are deleted as "self". It would be also reasonable to conclude that administration of the claimed polypeptides or cells expressing said polypeptides would not result in an efficacious vaccine as a T-cell response would not be evoked due to the process of clonal deletion in the thymus, rendering the host devoid of T-cells which are specific to the self-protein. Sarma et al (Journal of Experimental Medicine, 1999, Vol. 189, pp. 811-820) states that a critical issue in therapeutic regiments comprising the administration of tumor antigens for immunotherapy is whether unmutated tumor antigens which are expressed in normal cells impose special restrictions on the CTL response in vivo. Using transgenic mice wherein the antigen specific T cells specific for the P1A non-mutated tumor antigen are expressed at high levels and remain responsive to the P1A antigen when assayed in vitro, it was found that P1A antigen expressed in the thymus resulted in clonal deletion of said specific T-cells Sarma et al note that although said transgenic mice produce an overwhelming majority of T cells that are specific for P1A, said mice are no more resistant to cells expressing P1A than non-transgenic litter mates. Sarma et al concludes that even thought P1A can be a tumor rejection antigen, the effector function of P1A specific CTL is restrained in vivo and that these results have important implications for the strategy of tumor immunotherapy. With regard to the isolation of two T-cells which are specific for the instant antigen presented in the context of HLA-A24, it cannot be determined if this is a reliable indicator that in all patients, with any of the types of cancers listed on page 20, would have a T-cell available after thymic selection which would react with said antigen in the context of HLA-A24 or any other MHC molecule. Further, the presence of CTL which can lyse target cells in vitro has no apparent nexus with anti-tumor cytolytic activity in

vivo. Ohlen et al (Journal of Immunology, 2001, Vol.166, pp. 2863-2870) teach that T-cells recognizing normal proteins expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). These references serve to demonstrate that the lysis of target cells expressing a target tumor antigen in vitro does not constitute evidence that said T-lymphocytes would be effective at lysing tumor cells in vivo.It is noted that generic "cancers" would not be expected to initiate or maintain the same growth kinetics. This is of importance with regard to the teachings of Paul (ibid) on tumor cell escape mechanisms which include rapid growth as a means to overwhelm a slower immune response, (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4) and deficient antigen processing by tumor cells . With regard to the antigen processing, it is unclear whether all patients having a cancer expressing the disclosed antigen would have T-cells which were specific from the disclosed antigen, as the art teaches that the presence of a small number of tumor cells or the presence of a large number of tumor cells gives rise to tolerance (Paul, page 1166, second column, lines 19-23 under the heading "Sneaking Through"). Based on this observation, it is reasonable to conclude that a small number of slow growing tumor cells would elicit tolerance, and a large number of rapidly growing tumor cells would also elicit tolerance in line with the bi-phasic response reported by Paul. Thus, it appears that the interaction of the tumor cells with the host can produce tolerance by means of clonal deletion within the thymus of said host. Furthermore, the relationships between the multitude of different tumor cells exhibiting said antigen to the host would be variable as different types of organs (neuroblastoma, brain, colorectal, gastric, head-and neck, lung, prostate, breast, thyroid, bladder, kidney, leukemia, etc) and different histological types of neoplasms (carcinoma, squamous cell, mesothelial, neuroepithelial, sarcoma, leukemia, etc) all present said disclose antigen.

.Further, the claims are drawn to combinations of nucleic acids yielding non-specific peptide sequences. It is noted that Burch WO 03/084467 teaches that although putative epitopes

can be predicted using a computer to scan the sequence of the gene (antigen) for amino acid sequences that contain a "motif" or a defined pattern of amino acid residues associated with a particular MHC (HLA) allele and the "predicted" epitope sequences can then be synthesized and tested, the vast majority of epitope sequences which have been "predicted" to be immunogenic failed to be immunogenic in standard assays. Thus one of skill in the art would be forced into undue experimentation to find test all the epitopes encompassed by the instant claims..

It is concluded based on the references discussed above, that the state of the art with respect to treating patients with cancer by means of administering tumor antigen precursors or tumor antigens is unpredictable. The specification does not provide any disclosure that the administration of the claimed polypeptides would generate CTLs which lyse the cells of a tumor in situ, and it cannot be predicted based on the isolation of two T-cell clones specific for said antigen from a single patient having melanoma, that the group of patients having the cancers as indicated on page 20, would all have a T-cell repertoire that would include a T-cell specific for the disclosed self antigen. Without said T-cell in the repertoire of the host, presentation of said antigen by an antigen-presenting cell after vaccination with the disclosed polypeptide or cell expressing said disclosed polypeptide would not evoke a T-cell response, as the appropriate T-cell would not be available in the periphery to be activated by said antigen-presenting cell. Thus, without a demonstration that the administration of the claimed polypeptides or cells expressing said polypeptides overcomes immunosuppression of the host, the rapid growth of the target tumor cells, failure to access the tumor because of the stromal barrier and tolerance induction in the host and objective evidence that the target tumor cells in vivo present adequate tumor rejection antigen on the surface of all the tumor cells, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the claimed method of treatment.

Applicant argues that the rejection should be withdrawn as the instant claims are not directed to the immunotherapy of cancer and that the specification provides enablement for clams 62 abd 66 as claimed. This has been considered but not found persuasive. Applicant has not pointed to an alternative use of the expression vectors and host cells which would not be directed to immunotherapy. Accordingly the rejection is maintained.

Claims 56 and 133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 56 is drawn to an isolated nucleic acid molecule selected from the group consisting of (a) a fragment of a nucleic acid molecule having a nucleotide sequence as set forth as SEQ ID NO:23 of at least 23 nucleotides; and full length complements of (a), wherein the isolated nucleic acid sequence is not identical to SEQ ID NO:33. Claim 133 embodies the isolated nucleic acid of claim 56 wherein the fragment is 75, 100 or 200 custodies in length.

The instant claim 56 encompasses a genus of nucleic acid molecules which minimally comprise 50 contiguous nucleotides of SEQ ID NO:23. Claim 133 is further limiting, specify geneses which minimally comprise 75, 100 and 200 contiguous amino aid of SEQID NO:23. The genus is highly variant because it is not limited to molecules which encode the same protein as SEQ ID NO:23 as the fragment may be taken from any fragment of SEQ ID NO:23 without regard to coding sequence. The claim is drawn to a fragment "having" a nucleotide sequence of SEQID NO:23, rather than a fragment of SEQID NO:23, therefore the broadest reasonable interpretation dictates that the claimed fragments comprise rather than consist of nucleotide sequences of SEQ ID NO:23. The isolated nucleic acid molecules of the claims can differ substantially from the full length sequence of SEQ ID NO:23 because the claims permit the nucleic acid sequence to be comprised within a larger undisclosed sequence. The description of SEQ ID NO:23 fails to describe this claimed genus of nucleic acid sequences because the genus includes nucleic acid which code entirely different proteins from that of SEQ ID NO:23, especially in light of the fact that the reading frame can be altered from that of SEQ ID NO:23. One of skill in the art would reasonable conclude that applicant was not in possession of the claimed genus of isolated nucleic acids.

Claim 76 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a kit comprising isolated nucleic acid sequence consisting of SEQ ID

NO:27 and SEQ ID NO:28, does not reasonably provide enablement for a kit comprising a pair of isolated nucleic acids which consist essentially of 12-32 contiguous nucleotides of SEQ ID NO:23, nucleic acid molecules which differ from that of (a) due to codon degeneracy, and (c) complements of (a) or (b), wherein the pairs of isolated nucleic acid molecules do not overlap. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The instant claims are drawn to primer pairs. In order for said pair of primers to function in polymerase chain reaction, one member of the pair must be from the sense strand and the other member must be from the anti-sense strand. In the instant case, the claim allows for both primer to e be from the sense strand or both primers to be from the anti-sense strand. The specification has not taught a use for such a primer pair outside of the scope of PCR (page 19, line 26). The specification contemplates that an individual "unique" fragment can be used to generate fusion proteins for generating antibodies (page 19, lines 26-28). However, not all of the fragments encompassed by the primer pairs of the instant claim would be expected to make a useful antibody due to the requirement that the antibody epitope be accessible to interaction with an antibody molecule. Epitopes which are not accessible due to the three-dimensional configuration of the protein, or the presence of proteins which mask an intracellular epitope would not be expected to provide an antibody which can be used to detect the protein encoded by SEQ ID NO:23. Further, the claims include fragments of SEQ ID NO:23 without regard to the reading frame of SEQ ID NO:23 or the sense of anti-sense strand of SEQ ID BO:23, therefore a large number of the fragments encompassed by the claim would not encode a fragment of the protein encoded by SEQ ID NO:2

With respect to primers for PCR, Ashlock et al (Proceedings of the IEE Symposium on Computational Intelligence in Bioinformatics and Computational Biology, 2004, pp. 190-197) that out of a collection of 27408 hypothetical "correct" primer pairs 17224 amplify correctly while 10184 fail to amplify at all or amplify multiple targets (page 191, second column, lines 10-13). Thus, it cannot be expected that all of the primers encompassed by this claim will be useful for the polymerase chain reaction and one of skill in the art would be subjected to undue experimentation in order to use the broadly claimed primer pairs.

Claims 54, 60, 64 are allowed.

Claim 137 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
10/15/2006